

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

REVISED VERSION

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
8 January 2004 (08.01.2004)

PCT

(10) International Publication Number
WO 2004/002433 A1

(51) International Patent Classification⁷: A61K 31/52,
31/711, A61P 31/18

CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(21) International Application Number:
PCT/SE2003/001100

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(22) International Filing Date: 24 June 2003 (24.06.2003)

Published:
— with international search report

(25) Filing Language: English

(88) Date of publication of the revised international search report: 6 May 2004

(26) Publication Language: English

(15) Information about Correction:
see PCT Gazette No. 19/2004 of 6 May 2004, Section II

(30) Priority Data:
0202022-0 27 June 2002 (27.06.2002) SE
02024744.1 6 November 2002 (06.11.2002) EP

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(71) Applicant (for all designated States except US): MEDIVIR AB [SE/SE]; Lunastigen 7, S-141 44 Huddinge (SE).

(72) Inventor; and

(75) Inventor/Applicant (for US only): MÅRDH, Göran [SE/SE]; Karlavägen 71, S-114 59 Stockholm (SE).

(74) Agent: STRÖM & GULLIKSSON IP AB; Sjöporten 4, S-417 64 Göteborg (SE).

(81) Designated States (national): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,

WO 2004/002433 A1

(54) Title: SYNERGISTIC INTERACTION OF ABACAVIR AND ALOVUDINE

(57) Abstract: A pharmaceutical preparation comprising a synergistic combination of abacavir and alovudine and a pharmaceutical carrier therefor. Use of abacavir and alovudine together for the treatment of multiresistant HIV, wherein the use comprises simultaneous, combined or sequential administration of alovudine and abacavir.

519,332

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date
8 January 2004 (08.01.2004)

PCT

(10) International Publication Number
WO 2004/002433 A1

- | | | |
|----------------------------------------------------------------|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (51) International Patent Classification ⁷ : | A61K 3/52, | (81) Designated States (<i>national</i>): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW. |
| (21) International Application Number: | PCT/SE2003/001100 | |
| (22) International Filing Date: | 24 June 2003 (24.06.2003) | |
| (25) Filing Language: | English | |
| (26) Publication Language: | English | |
| (30) Priority Data: | | |
| 0202022-0 | 27 June 2002 (27.06.2002) | SE |
| 02024744.1 | 6 November 2002 (06.11.2002) | EP |
| (71) Applicant (<i>for all designated States except US</i>): | MEDI-VIR AB [SE/SE]; Lunastigen 7, S-141 44 Huddinge (SE). | |
| (72) Inventor; and | | |
| (75) Inventor/Applicant (<i>for US only</i>): | MÅRDH, Göran [SE/SE]; Karlavägen 71, S-114 59 Stockholm (SE). | |
| (74) Agent: | STRÖM & GULLIKSSON IP AB; Sjöporten 4, S-417 64 Göteborg (SE). | |

Published:— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/002433 A1

(54) Title: SYNERGISTIC INTERACTION OF ABACAVIR AND ALOVUDINE

(57) Abstract: A pharmaceutical preparation comprising a synergistic combination of abacavir and alovudine and a pharmaceutical carrier therefor. Use of abacavir and alovudine together for the treatment of multiresistant HIV, wherein the use comprises simultaneous, combined or sequential administration of alovudine and abacavir.

Synergistic interaction of abacavir and alovudine

Technical Field

- 5 This invention relates to the unexpected level of synergy exhibited between the HIV and HBV antivirals alovudine and abacavir against multiresistant HIV. The invention provides novel pharmaceutical preparations comprising the two agents in admixture or separately for concomitant or sequential administration and methods of treatment involving them.

10

Background to the Invention

- Alovudine (3'-deoxy-3'-fluorothymidine, FLT) is described in WO88/00088 as an antiviral active against HIV and HBV. Alovudine is a prodrug which is 15 converted in vivo to the active triphosphate.

Abacavir ((1R,4S)-9-[4-(hydroxymethyl)-2-cyclopenten-1-yl]guanine, carbovir) is described in EP 0434450 as having potent activity against HIV and HBV. Abacavir is also a prodrug which is converted in vivo to the active 20 triphosphate.

Alovudine and abacavir have each exhibited modest synergy with certain selected nucleosides, especially in in vitro tests (see for example US 5,571,798 and WO 00/16779). However, we have now discovered in the 25 clinical context that the particular combination of alovudine and abacavir produces a degree of antiviral synergy which is significantly greater than the usual level of synergy shown by the respective active agent.

Brief description of the invention

30

A first aspect of the invention provides a pharmaceutical preparation comprising a synergistic combination of abacavir and alovudine and a pharmaceutical carrier therefor.

A further aspect of the invention provides the use of abacavir and alovudine together for the treatment of HBV or especially multiresistant HIV, wherein the use comprises combined, concomitant or sequential administration of alovudine and abacavir.

5

The invention further provides a patient pack comprising alovudine and/or abacavir and an information insert containing directions on the use of both alovudine and abacavir together in combination.

- 10 The unexpectedly profound degree of antiviral synergy of the invention provides such benefits as more complete viral suppression, viral suppression over longer periods, limits the emergence of drug-escape mutations and thus the development of multiresistant HIV and HBV and allows better management of drug related toxicities. The use of this drug combination may, 15 in some circumstances decrease the number of pills taken by the patient and therefore increase patient compliance.

- It will be appreciated that the alovudine and abacavir combination of the invention may be administered simultaneously, either in the same or different 20 pharmaceutical composition, or sequentially. In the case of sequential administration, the delay in administering the second active ingredient should not be such as to lose the synergistic benefit of the invention. Typically sequential administration will not involve delays of greater than 12 hours, preferably less than 1 hour, such as before and after a meal.

25

- Due its good tolerability, once day dosing and very small dosage/day, alovudine can advantageously be administered as an add-on to existing HAART regimes, such as therapies comprising one or two nucleoside analogues and a protease inhibitor and/or one or more NNRTIs. Such 30 permutations can be chosen from conventional HIV antivirals such as 3TC, ddI (2',3'-dideoxyinosine), nevirapine, delavirdine, efavirenz, ritonavir, kaletra, saquinavir, amprenavir, amprenavir phosphate, indinavir etc. Preferably the preexisting regime or concomitant antiviral does not include d4T.

For ease of administration the alovudine and abacavir are conveniently presented in the same unit dosage form, such as a capsule or tablet or in a fluid containing appropriate concentrations of the two active agents.

- 5 The amount of alovudine and abacavir necessary for suppression of HIV or HBV will, of course vary from patient to patient and is ultimately at the discretion of the medical practitioner taking account of such well known factors as body weight, route of administration, concomitant medication, age, gender and general condition and the nature and severity of the disease.

10

In general abacavir is dosed in the range of about 3 to about 120 mg/kg/day such as 1-90 mg/kg/day, preferably 5-60 mg/kg/day. Preferably the abacavir is present in an amount of 200-800 mg per unit dose, more preferably 300-500 mg per unit dose.

15

- In general alovudine is dosed in the range of about 0.001-0.5 mg/kg/day, preferably 0.005-0.15 mg/kg/day. Favoured regimes thus include 0.01-0.5 mg/kg/day, such as 0.05-0.12 mg/kg/day. Preferably the alovudine is present in an amount of 0.1-20 mg per unit dose, such as 0.5-10 mg per unit dose, especially 0.5-5 mg/unit dose, such as 2-5 mg per unit dose.

Alovudine and abacavir are conveniently administered once or twice a day, especially once per day.

- 25 The alovudine and abacavir are conveniently administered and/or presented in a weight ratio corresponding to their respective ED₅₀, for example in the ratio 1-10:200-800

- 30 Abacavir is commercially available and its production is extensively described in the patent and academic literature. Alovudine is conveniently prepared as described in EP 495 225 and EP 470 355.

Abacavir and alovudine, particularly at the dosage rates herein described, are readily formulated in conventional pharmaceutical carriers and with

conventional excipients. The compounds of the invention are particularly suited to oral administration, but may also be administered rectally, vaginally, nasally, topically, transdermally or parenterally, for instance intramuscularly, intravenously or epidurally. The compounds may be administered alone, for 5 instance in a capsule, but will generally be administered in conjunction with a pharmaceutically acceptable carrier or diluent. The invention extends to methods for preparing a pharmaceutical composition comprising bringing alovudine and abacavir in conjunction or association with a pharmaceutically acceptable carrier or vehicle.

10

Oral formulations are conveniently prepared in unit dosage form, such as capsules or tablets, employing conventional carriers or binders such as magnesium stearate, chalk, starch, lactose, wax, gum or gelatin. Liposomes or synthetic or natural polymers such as HPMC or PVP may be used to 15 afford a sustained release formulation. Alternatively the formulation may be presented as a nasal or eye drop, syrup, gel or cream comprising a solution, suspension, emulsion, oil-in-water or water-in-oil preparation in conventional vehicles such as water, saline, ethanol, vegetable oil or glycerine, optionally with flavourant and/or preservative and/or emulsifier.

20

Brief description of the drawings

An embodiment of the invention will be illustrated by way of example only with reference to the drawings in which:

25 Figure 1 depicts median reduction in viral load in patients treated with the synergistic combination of the invention comprising alovudine added to an abacavir-containing regimen; in contrast to patients treated with alovudine and a non-abacavir-containing regimen.

Figure 2 depicts reduction in viral load in a comparative experiment in which 30 an alovudine /ddl-containing regimen is plotted beside an alovudine/non-ddl regimen.

Figure 3 depicts HIV suppression as a function of antiviral concentration for alovudine, abacavir or the 1:200 combination.

Detailed description of the inventionExample 1 Clinical Trial

- 5 A phase IIa trial was performed with 15 patients failing their current NRTI-containing regimens. Each patient had HIV RNA > 1000 cp/ml, with at least 2 mutations in the viral RT induced by previous viral therapy, as established by genotypic assay. Patients had a baseline viral load of $3.93 \log_{10}$ cp/ml.
- 10 The patients were administered qd 7.5 mg alovudine in a conventional carrier in addition to their current regimen for four weeks. The current regimes included various permutations of 3-5 HIV antivirals selected from 3TC, ddI, D4T, nevirapine, DMP, ritonavir, kaletra, saquinavir, amprenavir and indinavir, administered in their conventional dosage forms and regimens.
- 15 Antiviral load evaluation was performed weekly and then four weeks after discontinuation of alovudine. The alovudine addition was generally well tolerated and there was no withdrawal from therapy and no serious adverse events. A transient mean increase in CD4 counts of +52 counts/mm³ was detected.
- 20 The results are plotted in Figures 1 and 2. Referring initially to Figure 1, it will be apparent that the alovudine/abacavir-containing regimen results in significantly lower median viral loads compared to patients administered with alovudine but whose concomitant regimen did not include abacavir. This
- 25 profound reduction in viral load with alovudine/abacavir of the invention is surprising when contrasted with the performance of alovudine and ddI (didanosine) regimes in Figure 2, plotted against non-ddI containing regimens. Alovudine and ddI show clear synergy in *in vitro* tests (Cox et al AIDS Res Hum Retrovir. 1994 (12):1275-9). As is seen in Figure 2, this
- 30 known synergy translates in the clinical setting to a 0.2-0.3 log reduction. In contrast the combination of the invention consistently resulted in 1-1.5 log reductions, which is a quantum jump in synergy bearing in mind the logarithmic scale used.

As this clinical trial was performed as an add-on therapy to the patients pre-existing regime, it will be appreciated that the alovudine qd was administered in a separate dosage form to the abacavir (typically bd) and other antivirals (typically administered 2-4 times per day).

5

Example 2 Cell culture experiments

The antiviral effects of MIV-310 in combination with other NRTIs on HIV-1 replication in MT4 cells were examined by the median effect method (Chao 10 and Talalay 1983). The assay was performed in microtiter plates with each well containing 10^5 cells and 20-50 tissue culture infective doses of HIV-1, IIIb. Each drug alone and a mixture of the drugs in a constant ratio were serially diluted in 2-fold steps and added to the wells in quadruplicates. The constant ratio is selected to reflect the relative potency of the drugs. For 15 example the potency of abacavir in cell culture is 200 times less than the potency of alovudine. Accordingly, within a mixture, the relative contribution of abacavir would be drowned by the potency of alovudine if the mixture was equimolar. At a ratio of 1:200 abacavir:alovudine the respective contributions of the two drugs become apparent and the additional activity due to synergy 20 is measurable. The anti-viral effect was measured day 5 using the XTT colorimetric method.

Figure 3 plots antiviral activity against concentration for alovudine (abbreviated to FLT on this graph) and abacavir (abbreviated to ABC on this 25 graph) or and the mixture of the two at 1:200. Dissecting the points of the alovudine: abacavir 1:200 curve, especially those around the ED₅₀, it is readily apparent that the antiviral activity of the mixture is greater than the sum of the contributions of the respective parts. For example, the triangle at 30 65% inhibition at 0.63uM reflects a mixture where the abacavir component is at 0.63 micromolar and the alovudine component is 1/200 of that, ie 0.003 micromolar. However, abacavir alone (diamonds) at 0.63 uM produces an inhibition of just 10%, whereas alovudine alone (squares) at 0.003 uM produces an inhibition of 27%. The sum of the components is thus 37%. In

comparison the mixture at these same concentrations produces 60% inhibition.

- The effective dose giving 50% reduction of virus replication, ED₅₀ (or ED₇₅,
 5 ED₉₀ etc) was calculated for single drugs and for the combinations and the Combination Index calculated by median effect (*ibid*) to equal

$$D_A / Dx_A + D_B / Dx_B + \alpha(D_A D_B) / (Dx_A Dx_B)$$

- where Dx_A is the concentration which provides a given activity of the compound A alone, D_A is the concentration of A in the mixture to provide the
 10 same inhibition, Dx_B and D_B apply similarly for compound B, and alpha is zero if the compounds are mutually exclusive or 1 if mutually exclusive.

- A combination index (CI) less than 1 indicates synergism, CI equal to zero indicates addition and a CI greater than 1 indicates antagonism. The
 15 combination indices for the combination of the invention in comparison to prior art combinations is tabulated in Table 1 below. Once again, the combinations have been tested at molar ratios reflecting their relative ED₅₀s in cell culture.

20 Table 1

Combination	Molar ratio	Combination Index		
		50% inhibition	75% inhibition	90% inhibition
FLT + stavudine (d4T)	1:40	0.94	0.96	0.99
FLT + zidovudine (AZT)	1:1	0.70	0.71	0.72
FLT + didanosine (ddl)	1:250	0.95	0.76	0.61
FLT + abacavir (ABC)	1:200	0.74	0.57	0.47

- The preferred alovudine combination in the prior art (US 5,571,798) is
 25 AZT/alovudine which in this experiment produces an average CI of 0.71 across the three levels tested. In contrast the combination of the invention produces an average CI of 0.59, ie a significantly more profound degree of synergy than is demonstrated in the prior art combination. Similarly, another favoured combination in US 5,571,798, ddl in conjunction with FLT produces

an average CI of 0.77, once again showing that the combination of invention produces synergies significantly more intense than the levels of synergy previously seen.

- 5 As the goal of most antiviral therapies is to maintain serum trough levels corresponding at least to an ED₉₀ to prevent the development of resistant mutants, synergistic performance at the higher end of the spectrum has the greatest advantage. It will be apparent from Table 1 that the relative CI between the combination of the invention and prior art combinations is
- 10 even better at ED₉₀ compared to the average figures cited in the immediately preceding paragraph.

Consistent with the clinical trial of Example 1, Table 1 indicates that stavudine (d4T) is a less favoured component to combine with alovudine and

- 15 did not exhibit any significant degree of synergy as measured by CI.

Claims

1. A pharmaceutical preparation comprising a synergistic combination of abacavir and alovudine and a pharmaceutical carrier therefor.
5
2. A preparation according to claim 1 wherein the alovudine is present in an amount of 1-10 mg per unit dose.
3. A preparation according to claim 2 wherein the alovudine is present in
10 an amount of 0.5-7.5 mg per unit dose.
4. A preparation according to claim 3 wherein the alovudine is present in an amount of 0.5-5 mg per unit dose.
- 15 5. A preparation according to claim 1, wherein the abacavir is present in an amount of 200-800 mg per unit dose.
6. A preparation according to claim 5, wherein the abacavir is present in an amount of 300-500 mg per unit dose.
20
7. A preparation according to claim 1, wherein the alovudine and abacavir are present in a weight ratio corresponding to their respective ED₅₀.
8. A preparation according to claim 1, wherein the alovudine and
25 abacavir are present in the ratio 1-10:200-800
9. A patient pack comprising alovudine and/or abacavir and an information insert containing directions on the use of both alovudine and abacavir together in combination.
- 30 10. Use of abacavir and alovudine together for the treatment of multiresistant HIV, wherein the use comprises simultaneous, combined or sequential administration of alovudine and abacavir.

11. Use according to claim 10, wherein the use comprises administration of a preparation as defined in any one of claims 1-8 or the patient pack of claim 9.

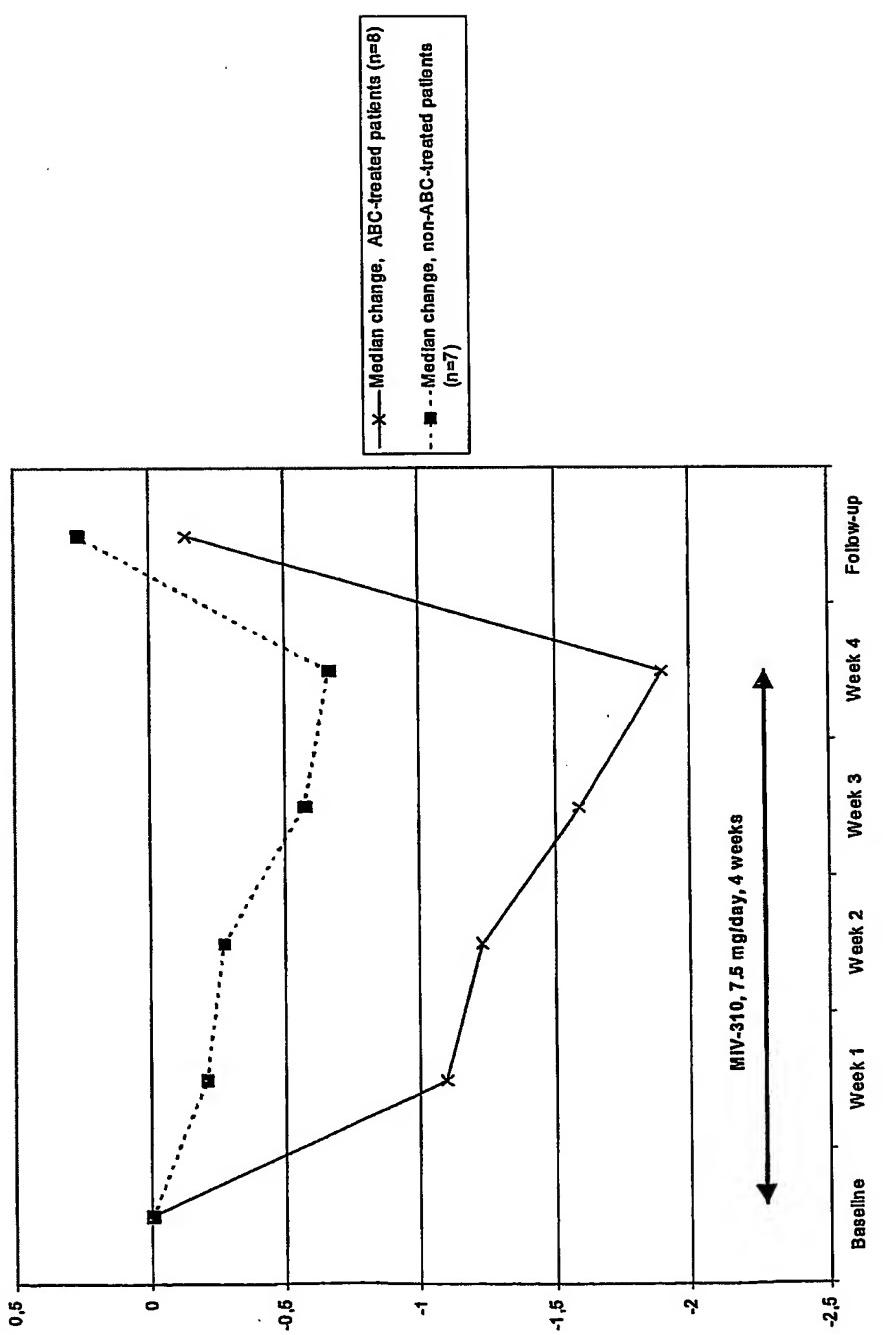


FIGURE 1

2/3

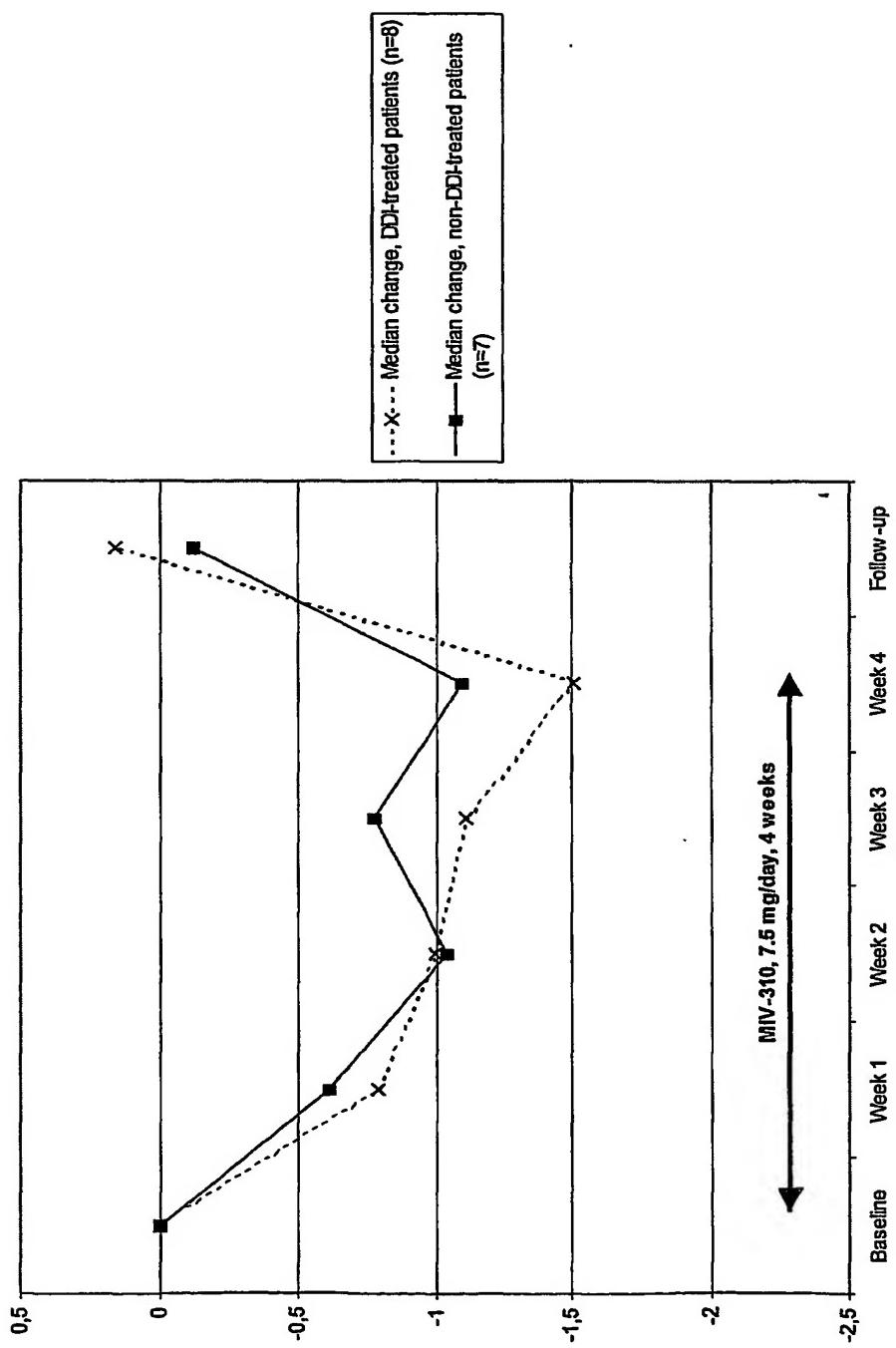


FIGURE 2

3/3

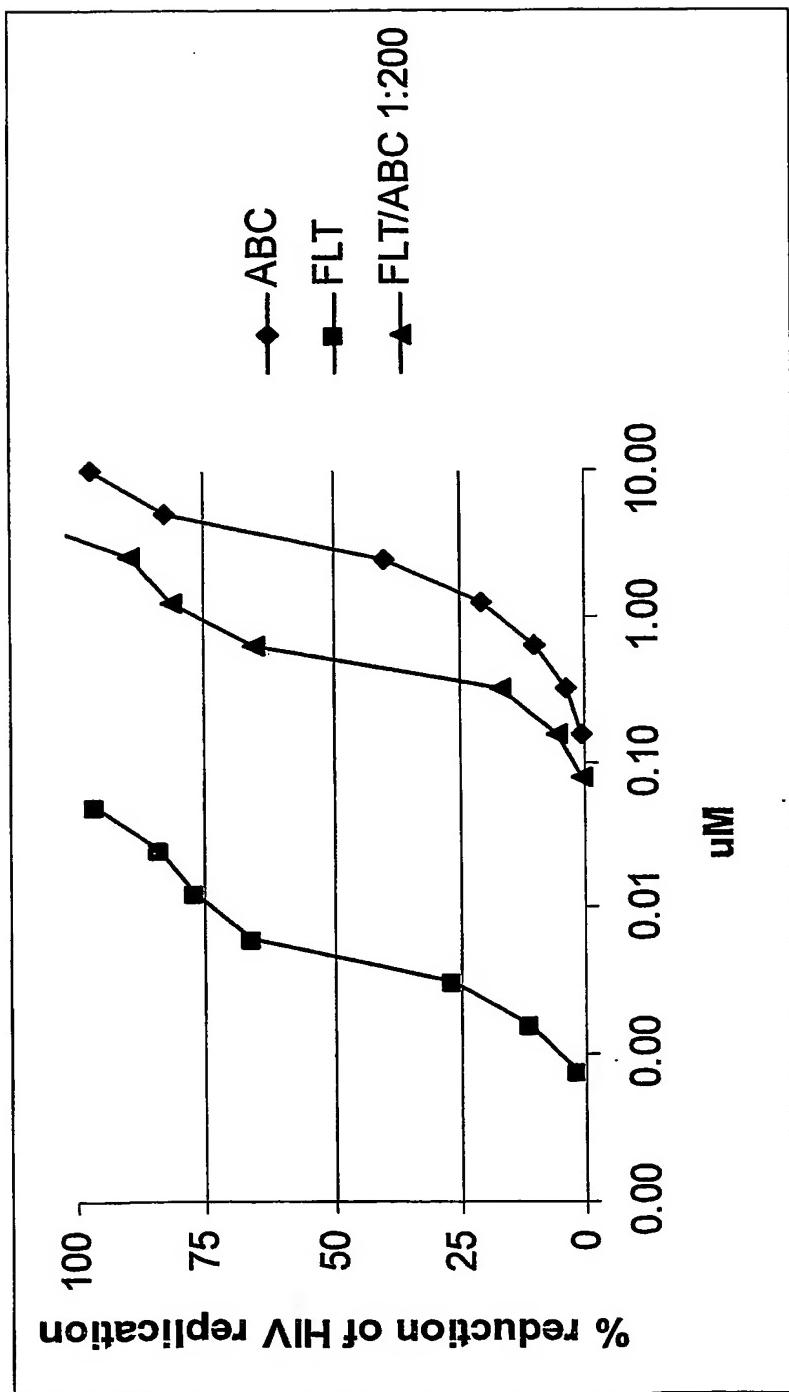


FIGURE 3

INTERNATIONAL SEARCH REPORT

International application No. PCT/SE 03/01100

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 3/52, A61K 31/711, A61P 31/18
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0346132 A1 (REGENETS OF THE UNIVERSITY OF MINNESOTA), 13 December 1989 (13.12.89) --	1-11
A	WO 0043014 A2 (EMORY UNIVERSITY), 27 July 2000 (27.07.00) --	1-11
A	WO 0016779 A1 (GLAXO GROUP LIMITED), 30 March 2000 (30.03.00) --	1-11
A	US 5571798 A (HARMBERG ET AL), 5 November 1996 (05.11.96) --	1-11

Further documents are listed in the continuation of Box C.

See patent family annex.

- * Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

24 Sept 2003

Date of mailing of the international search report

26 -09- 2003

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. + 46 8 666 02 86

Authorized officer

EVA JOHANSSON/BS
Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/SE 03/01100**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 8800050 A1 (ASTRA LÄKEMEDEL AKTIEBOLAG), 14 January 1988 (14.01.88) --	1-11
A	EP 0434450 A2 (THE WELLCOME FOUNDATION LIMITED), 26 June 1991 (26.06.91) -- -----	1-11

INTERNATIONAL SEARCH REPORT

Internat plication No.
PCT/SE03/01100

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **10 and 11**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/SE03/01100

Claims 10 and 11 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule. 39.1.(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

International application No., PCT/SE 03/01100

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0346132 A1	13/12/89	SE 0346132 T3 AT 73335 T 15/03/92 AU 627188 B 20/08/92 AU 3627289 A 14/12/89 DE 68900961 D 00/00/00 DK 284189 A 11/12/89 GR 3004628 T 28/04/93 JP 2091022 A 30/03/90 NZ 229453 A 27/08/91 US 5122517 A 16/06/92 ZA 8904392 A 29/08/90	
WO 0043014 A2	27/07/00	AU 2627000 A 07/08/00 BR 0007627 A 09/04/02 CA 2360039 A 27/07/00 CN 1337880 T 27/02/02 EP 1143976 A 17/10/01 IL 144382 D 00/00/00 JP 2002535278 T 22/10/02 NO 20013599 A 20/09/01	
WO 0016779 A1	30/03/00	AU 6085099 A 10/04/00 CN 1317971 T 17/10/01 EP 1113803 A 11/07/01 GB 9820417 D 00/00/00 JP 2002526449 T 20/08/02	
US 5571798 A	05/11/96	AT 132752 T 15/01/96 AU 630220 B 22/10/92 AU 6046990 A 22/02/91 CA 2063417 A 20/01/91 DE 69024804 D,T 29/08/96 DK 482081 T 28/05/96 EP 0482081 A,B 29/04/92 ES 2083458 T 16/04/96 JP 3149179 B 26/03/01 JP 4506961 T 03/12/92 SE 464168 B,C 18/03/91 SE 8902568 A 20/01/91 WO 9101137 A 07/02/91 SE 9000487 D 00/00/00	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/01100

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8800050 A1	14/01/88	AT 68349 T	15/11/91
		AU 598575 B	28/06/90
		AU 7700587 A	29/01/88
		CA 1286991 A,C	30/07/91
		DE 3773892 A	21/11/91
		DK 92788 A	23/02/88
		DK 172617 B	01/03/99
		EP 0277151 A,B	10/08/88
		SE 0277151 T3	
		JP 1500193 T	26/01/89
		JP 2540576 B	02/10/96
		SE 8602981 D	00/00/00
		US 5446029 A	29/08/95
		US 6358934 B	19/03/02

INTERNATIONAL SEARCH REPORT

International	on No.
PCT/SE 03/01100	

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0434450 A2	26/06/91	SE 0434450 T3	
		AP 196 A	30/06/92
		AP 9000234 D	00/00/00
		AT 181917 T	15/07/99
		AU 633672 B	04/02/93
		AU 6841990 A	27/06/91
		CA 2033044 A	23/06/91
		CN 1028106 B	05/04/95
		CN 1054981 A	02/10/91
		CZ 283481 B	15/04/98
		CZ 283786 B	17/06/98
		CZ 9006583 A	12/11/97
		CZ 9202470 A	15/04/98
		DE 69033197 D,T	28/10/99
		DK 434450 T	31/01/00
		EP 0921114 A	09/06/99
		EP 0921121 A	09/06/99
		ES 2133138 T	01/09/99
		FI 105813 B	00/00/00
		FI 106461 B	00/00/00
		FI 906367 A	23/06/91
		FI 970666 A	17/02/97
		FI 20001175 A	16/05/00
		GR 3031100 T	31/12/99
		HK 1009600 A	00/00/00
		HU 219454 B	28/04/01
		HU 220067 B	28/10/01
		HU 220630 B	28/03/02
		HU 220668 B	29/04/02
		HU 908407 D	00/00/00
		HU 9902538 D	00/00/00
		HU 9902539 D	00/00/00
		HU 9902543 D	00/00/00
		IE 904652 A	17/07/91
		IL 96748 A	31/07/95
		JP 11158160 A	15/06/99
		JP 11343292 A	14/12/99
		KR 192994 B	15/06/99
		LU 90426 A	06/10/99
		MX 9203215 A	01/07/92
		NZ 236593 A	26/01/94
		PL 167097 B	31/07/95
		PL 288403 A	26/06/92
		PT 96321 A,B	30/09/91
		RU 2068849 C	10/11/96
		RU 2091386 C	27/09/97
		SG 49685 A	15/06/98
		SK 247092 A	11/06/99
		SK 280000 B	11/06/99
		SK 280216 B	08/10/99
		SK 658390 A	08/10/99
		TW 473466 B	00/00/00
		US 5206435 A	27/04/93
		ZA 9010365 A	26/08/92

REVISED
VERSION

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/01100

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/52, A61K 31/711, A61P 31/18
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0346132 A1 (REGENETS OF THE UNIVERSITY OF MINNESOTA), 13 December 1989 (13.12.89) --	1-11
A	WO 0043014 A2 (EMORY UNIVERSITY), 27 July 2000 (27.07.00) --	1-11
A	WO 0016779 A1 (GLAXO GROUP LIMITED), 30 March 2000 (30.03.00) --	1-11
A	US 5571798 A (HARMENBERG ET AL), 5 November 1996 (05.11.96) --	1-11

Further documents are listed in the continuation of Box C.

See patent family annex.

- * Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "B" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

4 December 2003

04-12-2003

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. + 46 8 666 02 86

Authorized officer

EVA JOHANSSON/BS
Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/SE 03/01100**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 8800050 A1 (ASTRA LÄKEMEDEL AKTIEBOLAG), 14 January 1988 (14.01.88) --	1-11
A	EP 0434450 A2 (THE WELLCOME FOUNDATION LIMITED), 26 June 1991 (26.06.91) -- -----	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/01100

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **10 and 11**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORTInternational Application No.
PCT/SE03/01100

Claims 10 and 11 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule. 39.1.(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/07/03

 International application No.,
PCT/SE 03/01100

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0346132 A1	13/12/89	SE 0346132 T3		
		AT 73335 T		15/03/92
		AU 627188 B		20/08/92
		AU 3627289 A		14/12/89
		DE 68900961 D		00/00/00
		DK 284189 A		11/12/89
		GR 3004628 T		28/04/93
		JP 2091022 A		30/03/90
		NZ 229453 A		27/08/91
		US 5122517 A		16/06/92
		ZA 8904392 A		29/08/90
-----	-----	-----	-----	-----
WO 0043014 A2	27/07/00	AU 2627000 A		07/08/00
		BR 0007627 A		09/04/02
		CA 2360039 A		27/07/00
		CN 1337880 T		27/02/02
		EP 1143976 A		17/10/01
		IL 144382 D		00/00/00
		JP 2002535278 T		22/10/02
		NO 20013599 A		20/09/01
-----	-----	-----	-----	-----
WO 0016779 A1	30/03/00	AU 6085099 A		10/04/00
		CN 1317971 T		17/10/01
		EP 1113803 A		11/07/01
		GB 9820417 D		00/00/00
		JP 2002526449 T		20/08/02
-----	-----	-----	-----	-----
US 5571798 A	05/11/96	AT 132752 T		15/01/96
		AU 630220 B		22/10/92
		AU 6046990 A		22/02/91
		CA 2063417 A		20/01/91
		DE 69024804 D, T		29/08/96
		DK 482081 T		28/05/96
		EP 0482081 A, B		29/04/92
		ES 2083458 T		16/04/96
		JP 3149179 B		26/03/01
		JP 4506961 T		03/12/92
		SE 464168 B, C		18/03/91
		SE 8902568 A		20/01/91
		WO 9101137 A		07/02/91
		SE 9000487 D		00/00/00

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/07/03

International application No.

PCT/SE 03/01100

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8800050 A1	14/01/88	AT 68349 T	15/11/91
		AU 598575 B	28/06/90
		AU 7700587 A	29/01/88
		CA 1286991 A,C	30/07/91
		DE 3773892 A	21/11/91
		DK 92788 A	23/02/88
		DK 172617 B	01/03/99
		EP 0277151 A,B	10/08/88
		SE 0277151 T3	
		JP 1500193 T	26/01/89
		JP 2540576 B	02/10/96
		SE 8602981 D	00/00/00
		US 5446029 A	29/08/95
		US 6358934 B	19/03/02

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/07/03

International application No.

PCT/SE 03/01100

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0434450 A2	26/06/91	SE 0434450 T3	
		AP 196 A	30/06/92
		AP 9000234 D	00/00/00
		AT 181917 T	15/07/99
		AU 633672 B	04/02/93
		AU 6841990 A	27/06/91
		CA 2033044 A	23/06/91
		CN 1028106 B	05/04/95
		CN 1054981 A	02/10/91
		CZ 283481 B	15/04/98
		CZ 283786 B	17/06/98
		CZ 9006583 A	12/11/97
		CZ 9202470 A	15/04/98
		DE 69033197 D, T	28/10/99
		DK 434450 T	31/01/00
		EP 0921114 A	09/06/99
		EP 0921121 A	09/06/99
		ES 2133138 T	01/09/99
		FI 105813 B	00/00/00
		FI 106461 B	00/00/00
		FI 906367 A	23/06/91
		FI 970666 A	17/02/97
		FI 20001175 A	16/05/00
		GR 3031100 T	31/12/99
		HK 1009600 A	00/00/00
		HU 219454 B	28/04/01
		HU 220067 B	28/10/01
		HU 220630 B	28/03/02
		HU 220668 B	29/04/02
		HU 908407 D	00/00/00
		HU 9902538 D	00/00/00
		HU 9902539 D	00/00/00
		HU 9902543 D	00/00/00
		IE 904652 A	17/07/91
		IL 96748 A	31/07/95
		JP 11158160 A	15/06/99
		JP 11343292 A	14/12/99
		KR 192994 B	15/06/99
		LU 90426 A	06/10/99
		MX 9203215 A	01/07/92
		NZ 236593 A	26/01/94
		PL 167097 B	31/07/95
		PL 288403 A	26/06/92
		PT 96321 A, B	30/09/91
		RU 2068849 C	10/11/96
		RU 2091386 C	27/09/97
		SG 49685 A	15/06/98
		SK 247092 A	11/06/99
		SK 280000 B	11/06/99
		SK 280216 B	08/10/99
		SK 658390 A	08/10/99
		TW 473466 B	00/00/00
		US 5206435 A	27/04/93
		ZA 9010365 A	26/08/92